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REMARKS

I. Preliminary Remarks

In the Office Action dated March 17, 2004, the Examiner rejected claims 1-4, 8, 9, 12, 23, and 26 under 35 U.S.C. § 102(b) as being anticipated by Davis et al., *Plant Molecular Biology* 6:23-32, 1986 (hereinafter, "Davis"), asserting that Davis teaches that acetic acid or acetate alone is an elicitor. Additionally, the Examiner rejected claims 1-4, 7-21, 23, 25, and 26 under 35 U.S.C. § 103(a) over Davis in view of Stevens et al. (extraction of flavonoids from plants), and U.S. Pat. No. 3,810,990 (Jurd et al.; hereinafter, "Jurd") (assaying therapeutically active flavonoids). Further, the Examiner rejected claims 1-4 and 6-26 under 35 U.S.C. § 103(a) over Davis and U.S. Pat. No. 4,871,574 (Yamazaki et al.; hereinafter, "Yamazaki") (macerating plant material to obtain therapeutics). Claims 1-4 and 6-26 are currently pending and stand rejected.

II. Patentability Arguments

A. The Claims Are Novel Over Davis

The Examiner rejected claims 1-4, 8, 9, 12, 23, and 26 under 35 U.S.C. § 102(b) over Davis, asserting that the reference discloses the use of acetic acid or acetate alone as an elicitor. Office Action at pages 2-3. The Examiner further asserted that Davis discloses a method for eliciting antimicrobial phytoalexin compounds from soybean plants wherein the method comprises contacting living plants or cotyledons with an acetic acid buffer in amounts (e.g., 0.1%, or more than 12 mM; Fig. 6) effective to elicit and to recover phytoalexins into the aqueous medium. *Id.* at 3. In response, Applicant respectfully disagrees with the Examiner's position.

The Examiner relied on Fig. 6 of Davis for a disclosure of an effective amount of an acetic acid buffer being used to elicit phytoalexins from soybean plants. Fig. 6 of Davis, however, does not show that data relating to an "acetic acid" buffer; rather, the data relate to the use of a "sodium acetate/bicarbonate buffer" (*see* legend to Fig. 6 of Davis). Davis presents Fig. 6 to show the "[e]ffect of sodium acetate on the elicitor activity of hexa- β -glucosyl glucitol." (*Id.*) Importantly, Davis expressly states in that legend that "since . . . bicarbonate was not necessary for promotion of the elicitor activity of the hexa- β -glucosyl glucitol . . . , only the sodium acetate concentration is shown in the figure." (*Id.*) Thus, the control graph of Fig. 6 (open symbols) illustrates the effect of different concentrations of the

sodium acetate/bicarbonate buffer on the elicitor activity of a 10 ng/ml solution of hexa- β -glucosyl glucitol. While the legend explains that the bicarbonate component of the buffer had no effect on the hexa- β -glucosyl glucitol elicitor activity, and for that reason Fig. 6 only shows the concentration of sodium acetate in the buffer, that shorthand reference to the buffer is only relevant to effects on hexa- β -glucosyl glucitol elicitor activity. Neither the figure nor its legend attributes an elicitor activity directly to sodium acetate or bicarbonate. Moreover, the figure uses multiple filled symbols and open symbols without adequate identification. Further, no significance is attached to the relatively modest slope of the curve identified in Davis as a control curve relative to the curve identified in Davis as demonstrating the elicitor activity of hexa- β -glucosyl glucitol. Applicant respectfully submits Fig. 6 does not provide an enabling disclosure of the phenomena that Davis purports to disclose in that figure, or that the Examiner characterizes Davis as disclosing in that figure.

Consistent with the preceding clarification of the data disclosed in Fig. 6, the abstract of Davis identifies "specific elicitors" in the form of "hexa- β -glucosyl glucitol," "endopolygalacturonic acid lyase," and "oligogalacturonides" as inducing soybean cotyledons to accumulate phytoalexins. The abstract continues, noting that "the elicitor-active hexa- β -glucosyl glucitol acts synergistically with several biotic and abiotic elicitors in the induction of phytoalexins in soybean cotyledons." In contrast, the abstract subsequently identifies dilute solutions of cell-damaging buffers, including sodium acetate buffers. These "buffers" are identified as a class of compounds distinct from the "specific elicitors," the "biotic elicitors," and the "abiotic elicitors" referenced earlier in the abstract. The "specific elicitors" are expressly identified in the abstract of Davis, as noted above, while Davis states that "[a]biotic elicitors include detergents and heavy metal salts, such as HgCl_2 " (pages 23-24) and "[b]iotic elicitors include a variety of compounds isolated from microorganisms and plant tissues" (page 24). Moreover, in a section of the reference entitled "*Sources of phytoalexin elicitors*," Davis describes the sources of hexa- β -glucosyl glucitol, sodium polypectate fragments, and high molecular weight glucans, but not sodium acetate, or acetic acid. See pages 24-25. Thus, Davis itself is not identifying acetate compounds as elicitors, but rather as buffers.

Further confirmation that Davis is not disclosing acetate, or acetic acid, as an elicitor of therapeutics in plants is found in the Results section of the paper. Davis states that "the stimulation of elicitor activity by sodium acetate was specific for the hexa- β -glucosyl glucitol; sodium acetate did not stimulate the elicitor activity of either PGA lyase or the

decagalacturonide (data not shown)." Davis, page 28. If sodium acetate itself were an elicitor, one would expect it to be active in the presence of any of the aforementioned compounds. Davis recognized that sodium acetate was not an elicitor, and carefully refrained from such a characterization.

Davis then addresses the potential effect that acetic acid might have on plant cells by noting that "[s]everal studies have demonstrated that certain organic acids, including acetic acid, are toxic to plant cells (8, 27, 33). We suggest that the increased elicitor activity of the hexa- β -glucosyl glucitol assayed in the presence of sodium acetate is due to cell damage and the subsequent release of a factor (perhaps an oligogalacturonide) that acts synergistically with the hexa- β -glucosyl glucitol in the induction of phytoalexin accumulation." Page 28. Consistently, Davis also states that "[t]his suggests that the ability of sodium acetate to enhance the induction of phytoalexins by the hexa- β -glucosyl glucitol may be due to cell damage caused by sodium acetate and subsequent release of oligogalacturonides that act synergistically with the hexa- β -glucosyl glucitol." Page 29. Davis further proposes that the released "oligogalacturonides act as signals of tissue damage" and "enhance the response of plant tissues to the elicitor-active molecules." Davis, abstract.

The express statements in Davis establish that the Davis reference did not disclose, expressly or inherently, that acetate (or acetic acid) was an elicitor of any compound in a plant. Rather, acetate apparently exhibited some specific enhancing effect on a particular elicitor, hexa- β -glucosyl glucitol, of phytoalexins in soybeans and that effect was ascribed to acetate damaging or killing plant cells, thereby releasing a compound that interacted with hexa- β -glucosyl glucitol in eliciting phytoalexin production in soybeans. Consequently, Davis does not disclose, expressly or inherently, the contacting of a living plant or plant part with an amount of acetic acid effective to induce the production of a compound from the plant or plant part.

Davis also fails to disclose an "intact plant or plant part" being contacted with an elicitor. In the section titled "*Assay for elicitor activity*," the reference expressly states that "[a] 90- μ l aliquot of the test solutions [containing candidate elicitors] was applied to the wounded surface of each of twenty cotyledons per trial." Davis, page 25; emphasis added. Davis further describes the assay as involving the spectrophotometric measurement of absorbance at A_{286} of "wound droplet solutions" relative to maximal absorption at A_{286} using the strongest known elicitor of phytoalexin. *Id.* That relative measurement is a measure of $A_{286}/A_{286\text{max}}$, as explained at page 25 of Davis. The elicitor activity reported in Fig. 6 on page

29 of Davis, upon which the Examiner has relied, was determined by measuring $A_{286}/A_{286\text{max}}$. Thus, the Examiner is relying on the disclosure of experimental results relating to a plant part (soybean cotyledon) that is not intact (it is wounded). Davis, therefore, fails to disclose an element of the claims in failing to disclose an "intact plant or plant part" being contacted with any compound, such as acetic acid.

Further, Davis addresses the production of phytoalexins in soybeans and discloses that the accumulation of those phytoalexins is measured spectrophotometrically (i.e., through absorbance readings and ratios thereof). Nowhere does Davis disclose, expressly or inherently, the recovery of those phytoalexins. In explaining the effect of sodium acetate on plant cells, Davis acknowledges that acetate may damage plant cells, thereby releasing a factor, perhaps an oligogalacturonide, that acts synergistically with hexa- β -glucosyl glucitol in eliciting phytoalexins from soybean. It is that factor that is released, not the product (phytoalexin) being elicited. One of skill would not expect a plant cell damaged to the point of releasing such a factor to be capable of producing or accumulating an elicited compound such as phytoalexin. Thus, Davis does not disclose the "release" of phytoalexins as maintained by the Examiner. Accordingly, Davis fails to disclose an element of the claims in failing to disclose the recovery of the produced compound from the plant or plant portion.

Finally, Applicant disagrees with the Examiner's assumption that 0.1% sodium acetate is the same as 0.1% acetic acid. It is well known in the art that acetic acid is a weak organic acid with an acid dissociation constant K of 1.85×10^{-5} (*see* University Chemistry, Third Ed., pp. 220-226 (B.H. Mahan, ed.; Addison-Wesley Publishing Co., Reading, Mass., 1975), attached as Appendix A). The acid dissociation constant is a measure of acid strength and, for acetic acid, is determined as follows: $K = ([\text{H}_3\text{O}^+][\text{acetate anion}]) / [\text{acetic acid}]$, where the square brackets indicate concentrations. Thus, the acid dissociation constant for acetic acid is $K = 1.85 \times 10^{-5} = ([\text{H}_3\text{O}^+][\text{acetate anion}]) / [\text{acetic acid}]$. The product of the ion concentrations of dissociated acetic acid is much less than the concentration of undissociated acetic acid, consistent with the recognition of that acid as a weak acid. Further, when considering an acetate salt such as sodium acetate, one must also consider the influence of the paired ion (e.g., sodium) on the equilibrium position. The conversion of sodium acetate to acetic acid involves the concomitant formation of NaOH, a very strong base. As a very strong base, NaOH is almost completely dissociated under most conditions. The presence of the sodium and hydroxide ions affects the equilibrium position of sodium acetate and acetic acid, shifting the equilibrium position towards sodium acetate. Therefore, very little sodium acetate is

converted to acetic acid because of the necessary co-production of NaOH, which strongly tends to dissociate. Accordingly, it is scientifically unreasonable to assert that 0.1% sodium acetate is the same as 0.1% acetic acid.

For all of the foregoing reasons, Applicant respectfully submits that Davis is defective in not disclosing, expressly or inherently, each element of any one of the presently pending claims. At a minimum, (1) Fig. 6 of Davis does not disclose that sodium acetate is an elicitor of phytoalexins in soybean, (2) Davis does not disclose the recovery of any elicited product, and (3) neither Davis nor the art discloses that sodium acetate and acetic acid can be quantitatively interconverted. Accordingly, the Office has failed to establish a *prima facie* case of anticipation for any of the pending claims under 35 U.S.C. § 102(b) over Davis and the rejection should be withdrawn.

B. The Claims Are Non-obvious Over Davis in View of Secondary References

The Examiner also rejected claims 1-4, 8-9, 12, 23, and 26 under 35 U.S.C. § 103(a) over Davis, in view of Stevens et al., *Phytochemistry*, 39(4):805-813 (1995) (isolation of therapeutic flavonoids from leaf cuticle; hereinafter "Stevens") and U.S. Pat. No. 3,810,990 (antimicrobial activity of flavonoids; hereinafter "Jurd") and/or Yamazaki et al. (maceration of plant materials; hereinafter "Yamazaki"). In support, the Examiner relied on Davis for the proposition established above in addressing the novelty of the pending claims (i.e., "the use of acetic acid as a plant elicitor"). Office Action at page 4. The secondary reference, Stevens, was relied on for disclosures that therapeutic flavonoids may be extracted from leaf cuticle. Office Action at pages 4-6.

Applicant respectfully traverses the rejection. The Examiner's reliance on Davis as the primary reference is misplaced because (1) Fig. 6 of Davis does not disclose or suggest that sodium acetate (or acetic acid) is an elicitor of phytoalexins in soybean, (2) neither Davis nor the art discloses or suggests that sodium acetate and acetic acid can be quantitatively interconverted; and (3) Davis does not disclose or suggest the recovery of any elicited product. The secondary reference, Stevens, that was cited by the Examiner does not remedy any of the deficiencies of Davis.

Stevens is cited for the proposition that flavonoid anti-microbials can be extracted from plants to provide a chemical library of chemical therapeutics. Office Action at page 4.

Stevens does not disclose or suggest the use of an elicitor, such as the acetic acid recited in the pending claims. Stevens does not take issue with the settled principle that an acid and its component ions achieve an equilibrium state characterized by the acid dissociation constant (i.e., $K = ([H^+][anion])/[acid]$, for protic acids). Accordingly, Stevens does not disclose or suggest that sodium acetate can be quantitatively converted to acetic acid. Moreover, there is no motivation to combine Davis and Stevens. Davis teaches sodium acetate as a cell-damaging buffer that may release a compound that acts synergistically with hexa- β -glucosyl glucitol in eliciting the production of phytoalexins in soybean. Even if one were to misconstrue the remainder of the disclosure of Davis and accept that Davis teaches the use of acetic acid as a plant elicitor, one would not look to Stevens for a method of recovering an elicited product because Stevens does not teach the recovery of any product from plant cells damaged in the course of eliciting production of a compound. Accordingly, Applicant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness for the claimed subject matter in view of Davis and Stevens. Accordingly, the rejection of claims 1-4, 8-9, 12, 23, and 26 under § 103(a) over Davis in view of Stevens has been overcome.

The Examiner rejected claims 1-4, 8-9, 12, 22-23, and 26 under § 103(a) over Davis in view of Stevens and Jurd. Reliance was placed on Jurd as teaching assays of therapeutically active anti-microbial flavonoids by using culture turbidity or cell counts as a measure of cell viability. Again, Jurd does not remedy any of the above-noted deficiencies in the disclosure of Davis, and the Examiner has not maintained otherwise. Jurd does not disclose or suggest the use of sodium acetate, or acetic acid, as an elicitor of therapeutic compounds in intact plants or plant parts. Nor does Jurd disclose or suggest the quantitative interconversion of sodium acetate and acetic acid. Further, as for the asserted combination of Davis and Stevens, there is no proper motivation for combining Davis and Jurd. Jurd does not disclose or suggest a method of recovering a therapeutic compound from a plant cell following exposure of that cell to a cell-damaging agent such as acetic acid or sodium acetate. Accordingly, one would not look to Jurd for a method of recovering products produced using a method of eliciting erroneously attributed to the disclosure of Davis. Thus, the Office has failed to establish a *prima facie* case of obviousness for the claimed subject matter in view of Davis and Jurd. Accordingly, the rejection of claims 1-4, 8-9, 12, 22-23, and 26 under § 103(a) over Davis in view of Jurd has been overcome.

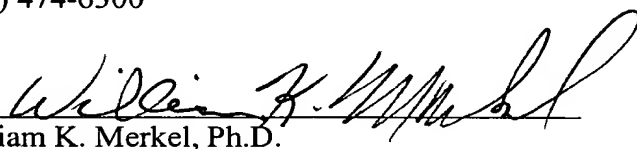
The Examiner rejected claims 1-4 and 6-26 under § 103(a) over Davis in view of Stevens, Jurd and Yamazaki, with Yamazaki being cited as teaching the maceration of plant materials to recover products found with such materials. Regardless of the accuracy of that characterization of Yamazaki, the Yamazaki reference does not remedy the deficiencies in the Davis disclosure noted above. Yamazaki does not disclose or suggest the use of sodium acetate, or acetic acid, as an elicitor of a therapeutic compound in an intact plant or plant part, and Yamazaki does not disclose or suggest the quantitative interconversion of sodium acetate and acetic acid under any set of conditions. Accordingly, Yamazaki, like Stevens and Jurd, does not remedy the deficiencies in the disclosure of Davis noted above, and the Examiner has not maintained otherwise. Therefore, the Office has not established a *prima facie* case of obviousness for the claimed subject matter in view of Davis and Yamazaki, and the rejection of claims 1-4 and 6-26 under § 103(a) over Davis in view of Yamazaki has been overcome.

For all of the foregoing reasons, Applicant respectfully submits that the rejection of claims 1-4, and 6-26 under 35 U.S.C. § 103(a) over Davis in view of Yamazaki should be withdrawn.

VI. CONCLUSION

In view of the remarks made herein, Applicant respectfully submits that claims 1-4 and 6-26 are in condition for allowance and respectfully requests expedited notification thereof.

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APPENDIX A

UNIVERSITY CHEMISTRY

Third Edition

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Since $[\text{H}_3\text{O}^+] = 0.1 \text{ M}$,

$$[\text{OH}^-] = \frac{10^{-14}}{[\text{H}_3\text{O}^+]} = \frac{10^{-14}}{10^{-1}} = 10^{-13} \text{ M}.$$

We see that in an *acidic* solution the concentration H_3O^+ is greater, and the concentration of OH^- less, than in pure water.

The calculation of the OH^- concentration can be used to further justify our assumption that the contribution of the self-ionization of water to the H_3O^+ concentration is negligible. The only source of OH^- in this solution is the self-ionization of water, and by the stoichiometry of reaction (6.3), one H_3O^+ is contributed for each OH^- . Therefore, the $[\text{H}_3\text{O}^+]$ contributed by the self-ionization of water is equal to $[\text{OH}^-]$, which we have seen to be 10^{-13} M . There is no question then that the contribution of the self-ionization of water to the H_3O^+ concentration is completely negligible.

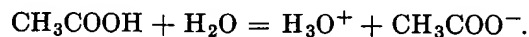
While we have used a solution of a strong acid as our example, it is clear that similar arguments can be applied to a solution of a strong base. In a 0.01 M solution of NaOH , the contribution of the self-ionization of water to the concentration of OH^- is negligible, because it must be less than 10^{-7} M . Thus in this solution

$$\begin{aligned} [\text{OH}^-] &= 0.01 \text{ M}, \\ [\text{H}_3\text{O}^+] &= \frac{K_w}{[\text{OH}^-]} \\ &= \frac{10^{-14}}{10^{-2}} = 10^{-12} \text{ M}. \end{aligned}$$

These arguments concerning the importance of either the H_3O^+ or OH^- contributed by water relative to the H_3O^+ or OH^- contributed by a dissolved acid or base are very important, for they are used repeatedly to simplify calculations dealing with weak acids and bases. Briefly, we can say that if a dissolved acid itself contributes a concentration of H_3O^+ equal to or greater than 10^{-6} M , the contribution of water to the total H_3O^+ concentration is negligible. A similar statement can be made about bases and the OH^- concentration.

Weak Acids and Bases

Now let us attack the problem of calculating the concentration of H_3O^+ in a pure aqueous solution of a weak acid. Acetic acid is a common laboratory reagent, and is often taken as a "typical" weak acid. The equilibrium we deal with then is



Let us abbreviate the formulas for acetic acid and the acetate ion to HOAc

and OAc^- , respectively. Then the equilibrium constant for the ionization is

$$\frac{[\text{H}_3\text{O}^+][\text{OAc}^-]}{[\text{HOAc}]} = K = 1.85 \times 10^{-5}. \quad (6.5)$$

The magnitude of this equilibrium constant lies roughly in the middle of the range of values that apply to weak acids, and this is the reason acetic acid is considered a typical weak acid.

Suppose we have a solution made up by adding C_0 moles of pure acetic acid to enough water to make one liter of solution. Some of this acid will dissociate to H_3O^+ and OAc^- , leaving behind an unknown concentration of undissociated acid. Our problem is to calculate the equilibrium concentrations of H_3O^+ , OAc^- , and HOAc by using the ionization-constant expression, Eq. (6.5). To do this we must take an equation in three unknowns, and convert it to an equation in one unknown.

The method we shall use is an intuitive approximate procedure. First, recognize that there are two sources of H_3O^+ : the ionization of the acid, and the self-ionization of water. But our experience is that the latter source is often unimportant compared with the former, at least when we deal with solutions of strong acids. As a trial procedure then, let us assume that all the H_3O^+ in solution comes from the ionization of the acid. As an immediate consequence, the stoichiometry of the ionization reaction tells us that

$$[\text{H}_3\text{O}^+] = [\text{OAc}^-], \quad (6.6)$$

since the only source of either of these ions is a reaction which produces them in equal amounts.

Equation (6.6) allows us to convert Eq. (6.5) into an equation in two unknowns. To complete the solution, one more relation is necessary. To obtain it, we recognize that the ionization equilibrium constant is small, and that consequently very little H_3O^+ and OAc^- can exist in equilibrium with undissociated HOAc . This suggests that to a good approximation, the equilibrium concentration of HOAc is the same as C_0 , the concentration that would be present if no HOAc dissociated. Therefore as our second assumption we have

$$[\text{HOAc}] = C_0. \quad (6.7)$$

Now let us calculate $[\text{H}_3\text{O}^+]$ for three different values of C_0 , and see whether our assumptions are justified in typical situations. First we choose $C_0 = 1 \text{ M}$. Then Eqs. (6.5), (6.6), and (6.7) give us

$$\begin{aligned} K &= \frac{[\text{H}_3\text{O}^+][\text{OAc}^-]}{[\text{HOAc}]} \cong \frac{[\text{H}_3\text{O}^+]^2}{C_0}, \\ [\text{H}_3\text{O}^+] &\cong (C_0 K)^{1/2} = (1 \times 1.85 \times 10^{-5})^{1/2} \\ &\cong 4.3 \times 10^{-3} \text{ M}. \end{aligned}$$

This answer is not exact, because we made two approximations in deriving it. However, we can use this approximate answer to check to see if our assumptions were justified.

Our first assumption was that the H_3O^+ contributed by the ionization of water was negligible compared with that derived from the acid. The concentration of H_3O^+ from the ionization of water cannot be greater than $10^{-7} M$, and this is much smaller than $4.2 \times 10^{-3} M$, so our first assumption and the approximation that $[\text{H}_3\text{O}^+] = [\text{OAc}^-]$ are justified.

Our second assumption was that very little of the HOAc dissociated, so that $C_0 \cong [\text{HOAc}]$. Strictly, however, the concentration of HOAc at equilibrium is given by

$$[\text{HOAc}] = C_0 - [\text{OAc}^-] \cong C_0 - [\text{H}_3\text{O}^+].$$

But $C_0 = 1 M$, and $[\text{H}_3\text{O}^+] \cong 4.3 \times 10^{-3}$. Therefore, our second assumption is justified and the approximation that $C_0 \cong [\text{HOAc}]$ is accurate to better than one percent.

Now let us try out our approximations in the situation where $C_0 = 0.01 M$, a rather dilute solution of acetic acid. Once again, assuming that

$$\begin{aligned} [\text{H}_3\text{O}^+] &= [\text{OAc}^-], \\ C_0 &= [\text{HOAc}] = 0.01 M, \end{aligned}$$

we get

$$\begin{aligned} \frac{[\text{H}_3\text{O}^+][\text{OAc}^-]}{[\text{HOAc}]} &\cong \frac{[\text{H}_3\text{O}^+]^2}{C_0} = K, \\ [\text{H}_3\text{O}^+] &\cong (C_0 K)^{1/2} = (10^{-2} \times 1.85 \times 10^{-5})^{1/2} \\ &\cong 4.3 \times 10^{-4} M. \end{aligned}$$

Now we must check the validity of our assumptions. As we have argued before, the concentration of H_3O^+ contributed by the self-ionization of water is less than $10^{-7} M$, and this is considerably smaller than $4.3 \times 10^{-4} M$. Therefore, our assumption that $[\text{H}_3\text{O}^+] = [\text{OAc}^-]$ is justified.

The validity of the second assumption depends on the concentration of H_3O^+ being much less than C_0 , for only then can we say that $C_0 \cong [\text{HOAc}]$. But we see that $[\text{H}_3\text{O}^+]$ is as large as 4% of C_0 , and therefore there is some question as to whether we were justified in assuming that $[\text{HOAc}] = 0.01 M$. However, while we have made an error of about 4% in the concentration of HOAc, the resulting error in the concentration of H_3O^+ is less than this because the concentration of H_3O^+ depends only on the *square root* of the HOAc concentration. Furthermore, in practical laboratory situations we are rarely interested in knowing the concentration of H_3O^+ to better than a few percent, so our second assumption is satisfactory in this case, if only marginally.

Our experience now suggests that if we try to calculate $[\text{H}_3\text{O}^+]$ for a solution of acetic acid in which $C_0 = 0.001 M$, at least one of our simplifying assump-

tions will break down. Let us see how serious the failure is, and what can be done about it. We assume that $[\text{H}_3\text{O}^+] = [\text{OAc}^-]$ and $[\text{HOAc}] = C_0 = 10^{-3} M$, and find

$$[\text{H}_3\text{O}^+] \cong (C_0 K)^{1/2} = (1.85 \times 10^{-5} \times 10^{-3})^{1/2} \\ \cong 1.36 \times 10^{-4} M.$$

Now there is no question that the first assumption is justified, but our answer shows that $[\text{H}_3\text{O}^+]$ is *not small* compared with C_0 , so the assumption that

$$[\text{HOAc}] = C_0 - [\text{H}_3\text{O}^+] \cong C_0$$

is not justified. The error in the HOAc concentration is greater than 10%, and the resulting error in the H_3O^+ concentration is several percent.

There are two ways by which we can avoid this difficulty. One is to use the accurate relation

$$[\text{HOAc}] = C_0 - [\text{H}_3\text{O}^+], \\ C_0 = 10^{-3} M$$

in the equilibrium constant, along with $[\text{H}_3\text{O}^+] = [\text{OAc}^-]$. This gives us

$$\frac{[\text{H}_3\text{O}^+][\text{OAc}^-]}{[\text{HOAc}]} = \frac{[\text{H}_3\text{O}^+]^2}{C_0 - [\text{H}_3\text{O}^+]} = K,$$

which is a quadratic equation in $[\text{H}_3\text{O}^+]$. Let us rearrange it to

$$[\text{H}_3\text{O}^+]^2 + K[\text{H}_3\text{O}^+] - C_0 K = 0,$$

and solve it by the quadratic formula

$$[\text{H}_3\text{O}^+] = \frac{-K \pm \sqrt{K^2 + 4KC_0}}{2}. \quad (6.8)$$

Inserting the values for K and C_0 gives

$$[\text{H}_3\text{O}^+] = 1.27 \times 10^{-4} M.$$

We see that this answer is nearly 7% less than our approximate answer.

From Eq. (6.8) we can deduce the condition for the validity of our approximate expression for $[\text{H}_3\text{O}^+]$. If, in Eq. (6.8), $K \ll C_0$, then $K^2 \ll 4KC_0$, in which case we have

$$[\text{H}_3\text{O}^+] = \frac{-K \pm \sqrt{K^2 + 4KC_0}}{2} \cong -\frac{K}{2} \pm \sqrt{KC_0},$$

and so if $K \ll C_0$, we can further simplify to

$$[\text{H}_3\text{O}^+] \cong \sqrt{KC_0},$$

which is our approximate expression for $[\text{H}_3\text{O}^+]$. We see then that in order for this approximation to be valid, the acid must be weak (K small) and fairly concentrated (C_0 large).

The second way to handle problems in which the simplifying assumptions prove inaccurate is to proceed by successive approximations to the correct answer. In our present example, our guess that $[\text{HOAc}] = C_0$ proved inaccurate. Let us use the approximate value of H_3O^+ that we found at first to improve our guess of the HOAc concentration. We have

$$[\text{HOAc}] = C_0 - [\text{H}_3\text{O}^+]$$

and $[\text{H}_3\text{O}^+] \cong 1.36 \times 10^{-4}$. A second, or refined, approximation to $[\text{HOAc}]$ would be

$$[\text{HOAc}] \cong C_0 - 1.36 \times 10^{-4} = 8.64 \times 10^{-4} M.$$

Inserting this into the equilibrium constant gives

$$\frac{[\text{H}_3\text{O}^+]^2}{8.64 \times 10^{-4}} = 1.85 \times 10^{-5},$$

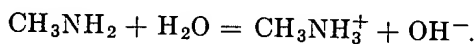
$$[\text{H}_3\text{O}^+] \cong 1.26 \times 10^{-4} M.$$

This second approximation to the H_3O^+ concentration is nearly the same as the "exact" value obtained from the solution of the quadratic equation. If we did not know the accurate answer to the problem, we could check the validity of this second approximation by using it to further refine our guess of $[\text{HOAc}]$, and repeating the calculation. If two successive answers differ negligibly, the final approximation is satisfactory.

Question. Use this second approximation of $[\text{H}_3\text{O}^+] = 1.26 \times 10^{-4}$ to obtain a third approximation for $[\text{H}_3\text{O}^+]$. What do you conclude from a comparison of the results of the second and third approximations?

It might seem that the successive approximation method is inferior to the exact solution via the quadratic equation. Actually, the successive approximation procedure is the more useful approach, since it is algebraically and arithmetically simpler, and can be applied to situations in which the exact approach would require the solution of a cubic or quartic equation.

To find the hydroxide ion concentration in a pure solution of a weak base, we make use of approximations very similar to those we have just discussed. The substance methyl amine is a weak base, capable of accepting a proton from water by the reaction



The corresponding equilibrium constant is

$$\frac{[\text{CH}_3\text{NH}_3^+][\text{OH}^-]}{[\text{CH}_3\text{NH}_2]} = K = 5.0 \times 10^{-4}.$$

which is our approximate expression for $[\text{H}_3\text{O}^+]$. We see then that in order for this approximation to be valid, the acid must be weak (K small) and fairly concentrated (C_0 large).

The second way to handle problems in which the simplifying assumptions prove inaccurate is to proceed by successive approximations to the correct answer. In our present example, our guess that $[\text{HOAc}] = C_0$ proved inaccurate. Let us use the approximate value of H_3O^+ that we found at first to improve our guess of the HOAc concentration. We have

$$[\text{HOAc}] = C_0 - [\text{H}_3\text{O}^+]$$

and $[\text{H}_3\text{O}^+] \cong 1.36 \times 10^{-4}$. A second, or refined, approximation to $[\text{HOAc}]$ would be

$$[\text{HOAc}] \cong C_0 - 1.36 \times 10^{-4} = 8.64 \times 10^{-4} M.$$

Inserting this into the equilibrium constant gives

$$\frac{[\text{H}_3\text{O}^+]^2}{8.64 \times 10^{-4}} = 1.85 \times 10^{-5},$$

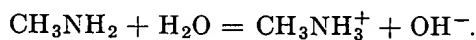
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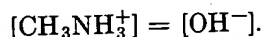


The corresponding equilibrium constant is

$$\frac{[\text{CH}_3\text{NH}_3^+][\text{OH}^-]}{[\text{CH}_3\text{NH}_2]} = K = 5.0 \times 10^{-4}.$$

What is the equilibrium concentration of hydroxide ion in a solution prepared by adding 0.1 mole of CH_3NH_2 to enough water to make one liter of solution?

To reduce the problem to one unknown, we make two assumptions. The first is that the concentration of OH^- contributed by the ionization of water is negligible compared with that contributed by the base. Therefore, by the stoichiometry of the ionization reaction



The second assumption is that most of the CH_3NH_2 remains as such, since the equilibrium constant for its conversion to CH_3NH_3^+ is small. Therefore, to a good approximation

$$[\text{CH}_3\text{NH}_2] = 0.1 - [\text{CH}_3\text{NH}_3^+] \cong 0.1 M.$$

Note carefully that these assumptions and approximations are exactly analogous to those made in the treatment of weak acid ionization. Using our two approximations and the equilibrium constant, we obtain an equation for $[\text{OH}^-]$:

$$K = \frac{[\text{CH}_3\text{NH}_3^+][\text{OH}^-]}{[\text{CH}_3\text{NH}_2]} = \frac{[\text{OH}^-]^2}{0.1} = 5.0 \times 10^{-4},$$

$$[\text{OH}^-] = 7.1 \times 10^{-3} M.$$

To justify our assumptions we note that $7 \times 10^{-3} M$ is much greater than $10^{-7} M$, which is the maximum OH^- concentration ever contributed by the self-ionization of water. The second assumption, that

$$[\text{CH}_3\text{NH}_2] \cong 0.1 M,$$

requires that

$$[\text{OH}^-] = [\text{CH}_3\text{NH}_3^+] \ll 0.1 M,$$

which is satisfied, but rather marginally. The validity of the second assumption depends on K being small and the concentration of the base being fairly large. A second approximation to $[\text{OH}^-]$ can be obtained by saying

$$[\text{CH}_3\text{NH}_2] \cong 0.1 - 7.1 \times 10^{-3} = 9.29 \times 10^{-2} M,$$

and

$$\frac{[\text{OH}^-]^2}{9.29 \times 10^{-2}} = 5.0 \times 10^{-4},$$

$$[\text{OH}^-] = 6.8 \times 10^{-3} M.$$

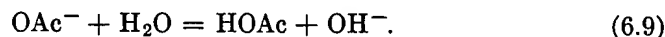
This answer differs only slightly from our first result, and therefore is a sufficient approximation for most purposes.

In this section we have discussed specific examples of acid-base equilibria to illustrate the general method by which similar problems can be solved. We have

avoided and will continue to avoid supplying general mathematical formulas which give an answer in one step. The reason for this is that any *simple* formula we might give would necessarily be approximate and might fail to apply in a given situation. The only way to be sure that an expression is appropriate for a given problem is to derive it following the procedures we have illustrated, taking full account of the chemical and physical peculiarities of the problem.

6.4 HYDROLYSIS

Hydrolysis is an aspect of acid-base equilibrium that traditionally is treated as a separate, distinct phenomenon, but in fact it requires no concepts beyond those we have already discussed. We have remarked that a weak acid and its anion are a conjugate acid-base pair, and that if an acid is weak, its conjugate base tends to be strong. For example, acetic acid is a moderately weak acid, so acetate ion is a moderately strong base, and will acquire protons in aqueous solution by the reaction



This reaction represents the hydrolysis of the acetate ion, but we can see that it is nothing more than the "ionization" of a weak base. Therefore it should be possible to calculate the hydroxide ion concentration in a pure solution of NaOAc in the same way that we calculated $[\text{OH}^-]$ in a pure solution of CH_3NH_2 .

There is one additional matter which must be dealt with. The equilibrium constant for reaction (6.9) is

$$\frac{[\text{HOAc}][\text{OH}^-]}{[\text{OAc}^-]} = K_h, \quad (6.10)$$

where K_h is called the hydrolysis constant. Hydrolysis constants are not often tabulated, because they can be evaluated easily from the ionization constants of the corresponding acid. To do this, we multiply Eq. (6.10) by $[\text{H}_3\text{O}^+]/[\text{H}_3\text{O}^+]$ to get

$$\frac{[\text{HOAc}][\text{OH}^-][\text{H}_3\text{O}^+]}{[\text{OAc}^-][\text{H}_3\text{O}^+]} = K_h.$$

In the numerator we recognize that the product $[\text{OH}^-][\text{H}_3\text{O}^+]$ is equal to K_w , the ion product constant for water. This gives us

$$\frac{[\text{HOAc}]K_w}{[\text{H}_3\text{O}^+][\text{OAc}^-]} = K_h,$$

and it is now easy to see that the remaining factors are equal to the reciprocal